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Neuroleptics in the Management of Delirium in Patients with Advanced Cancer

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Abstract

Purpose of review—Delirium is the most common and distressing neuropsychiatric syndrome in cancer patients. Few evidence-based treatment options are available due to the paucity of high quality of studies. In this review, we shall examine the literature on the use of neuroleptics to treat delirium in patients with advanced cancer. Specifically, we will discuss the randomized controlled trials that examined neuroleptics in the front line setting, and studies that explore second line options for patients with persistent agitation.

Recent findings—Contemporary management of delirium includes identification and management of any potentially reversible causes, coupled with non-pharmacological approaches. For patients who do not respond adequately to these measures, pharmacologic measures may be required. Haloperidol is often recommended as the first line treatment option, and other neuroleptics such as olanzapine, risperidone and quetiapine represent potential alternatives. For patients with persistent delirium despite first line neuroleptics, the treatment strategies include (1) escalating the dose of the same neuroleptic, (2) rotation to another neuroleptic, or (3) combination therapy (i.e., the addition of a second neuroleptic or other agent). We will discuss the advantages and disadvantages of each approach, and the available evidence to support each strategy.

Summary—Adequately powered, randomized trials involving proper control interventions are urgently needed to define the optimal treatment strategies for delirium in the oncology setting.

Keywords

delirium; haloperidol; treatment; neuroleptics; neoplasms; palliative care; prognosis

Introduction

Delirium is a common neuro-psychiatric complication in patients with advanced cancer [1-3], affecting over 50% of patients admitted to acute palliative care units (APCUs) [4] and up to 93% of cancer patients before death [5,6]. The cardinal features of delirium include

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Conflicts of interest

The authors report no relevant conflict of interest.

The pharmacologic agents discussed in this manuscript have not been approved by the FDA specifically for delirium management.

altered levels of consciousness, acute confusion, inattention, restlessness, impaired cognition, and perception abnormalities that fluctuate over the course of the day [7].

Approximately 50%-70% of patients with delirium have hyperactive or mixed subtypes that are characterized by agitation and are often associated with hallucinations, delusions, and hypervigilance [4]. Agitation, which ranges from restlessness to aggressive violent behavior, can pose a safety risk for patients, caregivers, and healthcare professionals and can be highly distressing to all involved, particularly the 50% of patients with persistent delirium that does not respond to standard treatment with low-dose haloperidol [8]. In a survey of 195 bereaved caregivers, 145 (74%) and 121 (62%) cancer patients were reported to have had restlessness and mood lability before death, respectively, which represented the main source of distress for caregivers [9]. In a separate study examining agitation in delirium, the mean delirium-related distress level was 3.2 of 4 for patients (with 4 being the most severe), 3.75 of 4 for caregivers, and 3.1 of 4 for nurses [10,11]. In patients with delirium, agitation and associated symptoms may impede their communication with their families and hinder their participation in treatment decisions, counseling, and symptom assessment [12]. Ultimately, delirium is associated with increased morbidity and mortality [13].

In the era of prognosis-based decision making [14], it is important to recognize that the prevalence, causes, treatment and outcomes associated with delirium may differ substantially depending on where the patient is along the disease trajectory (Figure 1). For instance, patients with years of survival often have reversible types of delirium (e.g. post-operative delirium) and may be preventable. In contrast, patients those with weeks to days of survival often do not recover from their terminal delirium, and controlling the agitation and minimizing distress may be the main therapeutic goal [15-17]. In addition to prognosis, other important factors to consider when interpreting the literature on delirium management include patient age (elderly vs. younger) and study setting (surgical units vs. medical units vs. intensive care units).

In this review, we examine the literature on the use of neuroleptics to manage delirium in the palliative cancer care setting. Because few studies have specifically been conducted in this patient population, we will include patients treated in the general medical units in this review. We will discuss the randomized controlled trials that examined neuroleptics in the front line setting, and studies that explore second line options for patients with persistent agitation.

Front Line Management of Delirium

The current management of delirium involves (1) identifying and removing any reversible causes, (2) providing non-pharmacologic interventions such as environmental control and orientation aids, and (3) administering pharmacologic treatments for palliation **CITE**. Pharmacologic measures include neuroleptics (e.g., haloperidol, chlorpromazine, olanzapine, risperidone, quetiapine) and benzodiazepines (e.g. lorazepam, midazolam) [18].

Few studies have evaluated the management of delirium in the medical setting outside of intensive care units, and only one published study to date has been conducted in the

palliative care setting [19] (Table 1). This landmark randomized controlled trial compared haloperidol (N=11), chlorpromazine (N=13), and lorazepam (N=6) for the first-line management of delirium in human immunodeficiency virus (HIV) patients [20]. The primary outcome, as assessed by the Delirium Rating Scale, improved with haloperidol (P<0.001) and chlorpromazine (P<0.001), and no significant differences were detected between the two neuroleptic arms (P=0.44). The lorazepam arm was terminated prematurely because of excessive drowsiness. Understandably, a 2012 Cochrane systematic review on drug therapy for delirium in terminally ill adult patients concluded that "there remains insufficient evidence to draw conclusions about the role of drug therapy in the treatment of delirium in terminally ill patients." [19]

A handful of clinical trials have examined the management of delirium with neuroleptics in the medical non-palliative care settings. Hu et al. conducted an open label trial comparing haloperidol, olanzapine and usual care in 175 patients, and reported that both haloperidol and olanzapine were associated with a reduction in the severity of delirium (Delirium Rating Scale reduction 70% vs. 72% vs. 30%, P<0.01). Subsequent randomized trials compared haloperidol to risperidone [22], olanzapine to risperidone [23], haloperidol, olanzapine and risperidone [26], and showed that these agents had similar efficacy. Tahir et al. compared quetiapine and placebo, and reported that delirium scores were similar between the two study arms over time; however, quetiapine was associated with a more rapid improvement over time [24].

More recently, Agar et al. conducted a randomized controlled trial comparing risperidone, haloperidol and placebo in 165 patients with life-limited illnesses and symptomatic delirium [27]. Subcutaneous midazolam 2.5 mg was used as a rescue medication in all arms. The preliminary analysis has been presented in abstract form only. The primary outcome was a composite of several delirium symptoms (inappropriate behavior, inappropriate communication, and illusions/hallucinations) assessed using the Nursing Delirium Screening Scale (NuDESC) at 72 hours. Surprisingly, both risperidone (0.57, 95% CI 0.17-0.98, p=0.006) and haloperidol (0.29, 95% CI 0.11-0.48, p=0.002) were associated with worse delirium symptoms. Furthermore, the neuroleptics arms required more midazolam rescue (p<0.05) and had poorer overall survival (p=0.03). These preliminary findings highlight the need to maximize nonpharmacologic measures. At the same time, it raises more questions about the pharmacologic management of delirium. Should neuroleptics be given at all, and if so for what indications and when? Were there subgroups with a more favorable risk-benefit ratio? What doses should be used to achieve the optimal risk-benefit ratio? Was midazolam an appropriate rescue medication in this setting? Clearly, further studies are needed to address these questions.

Haloperidol Dosing

Only a handful of non-randomized studies have examined the dosing of neuroleptics in the oncology setting specifically. Akechi et al. reported a case series of 10 hospitalized cancer patients seen by the psychiatry team [28]. Haloperidol was started at 0.5 mg parenterally or 0.75 mg orally. Patients were monitored 30 minutes after each dose, and haloperidol was titrated over 12 dose levels up to a maximum single dose of 5 mg parenterally if agitation or

disruptive behavior continued. The mean haloperidol dose was 6 mg (standard deviation [SD] 4 mg, range 0.5 mg to 11 mg) during the first day. The median duration of delirium was 6 days, and the average haloperidol daily dose until recovery of delirium was 5.4 mg (SD 3.4 mg).

In a retrospective study, Olofosson et al. examined the management of delirium for 90 consecutive cancer patients consulted by the psychiatry service [29]. A majority (66%) received haloperidol alone, and the reminder received either a combination of haloperidol and benzodiazepine (28%) or other medications (6%). Among the patients who had intravenous haloperidol, 41 patients received low doses (0.5-5 mg/day), 17 patients had moderate doses (6-20 mg/day) and 8 patients had high doses (>20 mg/day), with an overall mean dose of 10.9 mg/day. However, this study did not describe the titration scheme.

Other studies examined the use of neuroleptics in the palliative care setting. In a cohort of 100 consecutive patients with delirium admitted to an acute palliative care unit at a tertiary care cancer center, haloperidol was the most commonly used neuroleptic in the front line setting (94%), followed by olanzapine (8%) and chlorpromazine (5%) [4]. The median haloperidol equivalent daily dose (HEDD) was 1 mg (interquartile range [IQR] 0-3 mg), 3 mg (IQR 1-6 mg), 3 mg (IQR 1-8) mg, 4 mg (IQR 2-6.3 mg) and 4 mg (IQR 1-8 mg) for days 1, 2, 3, 4 and 5, respectively, with an average median HEDD of 3.2 mg/day (IQR 1.5-6 mg) during the first 5 days. 10, 59 and 31 patients had hyperactive, mixed and hypoactive delirium, respectively, and were given a median HEDD of 9.9 mg (IQR 4.3-12.9 mg), 4.0 mg (2.6-6.7 mg) and 1.5 mg (0.8-3.2 mg) ($P<0.001$).

Another prospective study focused on 99 patients who recovered from their delirium in the same acute palliative care unit [30]. The median HEDD was 2.5 mg (IQR 1-4.7 mg), which was ineffective in preventing delirium recall and related distress in a majority of patients. HEDD increased with greater distress related to patients' symptoms among nurses and palliative are specialists, suggesting that neuroleptic dose was influenced more by healthcare professional distress than by delirium symptom frequency.

Crawford et al. recently described the use of haloperidol for delirium in 119 patients (88% had cancer) recruited from 14 centers [31]. The average dose in the first 24 hours was 2.1 mg (SD 1.6 mg). At 48 hours, 42 (35%) had lower delirium scores as rated by the National Cancer Institute Common Toxicity Criteria, 52 (44%) had no change, 10 (8%) had worsening delirium and 10 (8%) died.

Taken together, the above studies indicate that the dose of haloperidol in routine practice varies widely (ranging between <1 mg/day and >20 mg/day), and was not clearly associated with improved outcomes. To date, no clinical trials have specifically compared between different doses of haloperidol for delirium in the medical setting. Thus, the therapeutic dose of haloperidol and the optimal dose titration schedule for delirium remain to be defined.

Management of Persistent Agitated Delirium

Because of the paucity of research, there is no standardized approach for the management of persistent agitated delirium despite non-pharmacologic measures and a trial of neuroleptics.

Clinicians caring for patients with persistent agitated delirium are faced with the dilemma of deciding among (1) escalating the dose of the same neuroleptic, (2) rotation to another neuroleptic, or (3) combination therapy (i.e., the addition of a second neuroleptic or other agent). Table 2 highlights the potential advantages and disadvantages of each approach.

Dose escalation

For patients who continued to experience persistent agitated delirium despite low to moderate doses of a neuroleptic (e.g. haloperidol 8 mg or less per day), one option may be to increase the dose of the same medication further. As discussed above, Akechi et al. employed a rapid titration scheme to personalize the dose of haloperidol for each patient and reported that delirium resolved in all patients with the duration of delirium ranging between 1 and 24 days [28]. The medication dose to achieve the optimal risk-benefit ratio likely varies among individual patients.

Neuroleptic rotation

Similar to opioid rotation for pain control, neuroleptic rotation represents an alternative to dose escalation for patients who did not respond to low/moderate dose neuroleptics (Table 2). Although multiple typical and atypical neuroleptics are available, chlorpromazine represents one of the few feasible second line options for patients with refractory delirium because (1) unlike olanzapine, risperidone, and quetiapine, it can be given intravenously, facilitating rapid administration and control of agitation (onset 15 minutes); (2) its α1 adrenergic blockage effect may be particularly useful for inducing sedation and treating agitation. Dexmedetomidine, which can *only* be used in the critical care setting to manage delirium, exerts its effect through both its α2 adrenergic agonist and α1 adrenergic antagonist activities [32-35]. To date, the Breitbart study remains the only delirium trial to examine chlorpromazine in the front line setting, and no published randomized controlled trial has specifically examined the use of neuroleptics in the second line setting or beyond [20].

One retrospective study has examined rotation from haloperidol to chlorpromazine for persistent delirium [36]. Among 128 APCU patients started on haloperidol for first line management of delirium with an initial median haloperidol dose of 5 mg (IQR 3-7 mg), 91 (71%) improved and were discharged alive while the remaining 37 (29%) patients with persistent delirium received chlorpromazine. The initial median chlorpromazine dose was 150 mg (IQR 100-150 mg), with an improvement observed in 13 (33%) of these individuals. These findings suggest that neuroleptic rotation may be a feasible option for refractory delirium, although randomized controlled trials are needed to confirm its efficacy. Rotation to other neuroleptics remains to be explored in future studies.

Rotation to olanzapine after haloperidol failure has also been studied. In a single-arm open label clinical trial, Elasayem et al. evaluated the safety and tolerability of scheduled subcutaneous olanzapine over 3 days for hyperactive or mixed delirium in cancer patients admitted to an APCU who did not respond to 10 mg or more of parenteral haloperidol [37]. Among the 24 participants, subcutaneous olanzapine 5 mg was given every 8 hours for 3 days with haloperidol for breakthrough agitation. The dose of olanzapine was increased to

10 mg every 8 hours if patients required more than 8 mg/day of rescue haloperidol. In a before and after comparison, both the Richmond Agitation Sedation Scale and the total dose of rescue haloperidol decreased, but not the Mini-mental State Examination. Olanzapine was generally well tolerated, although 4 patients developed severe toxicities (e.g., seizure, diabetes insipidus, hypotension, and paradoxical agitation); it was difficult to ascertain whether these side effects were associated with olanzapine without a control arm.

Combination therapy

Similar to the principles of opioid co-analgesia and multi-agent chemotherapy, combination neuroleptic therapy has potential merits (Table 2), although this has not been studied in randomized trials. Menza et al. compared 4 patients who received haloperidol alone to the 10 patients who had intravenous haloperidol and benzodiazepines [38], and reported significantly less extrapyramidal symptoms in the combination arm ($P<0.001$).

Theoretically, the addition of benzodiazepines to neuroleptic may also provide more rapid control of agitation and anxiety, thus decreasing delirium-related distress in patients, caregivers, and healthcare professionals. Furthermore, lorazepam may reduce delirium recall through its amnesic effect. Our research team is conducting a parallel, double-blind, randomized controlled trial comparing the use of lorazepam plus haloperidol versus placebo plus haloperidol for a single episode of agitation in cancer patients with mixed and/or hyperactive delirium admitted to the APCU (ClinicalTrials.gov Identifier: NCT01949662) (43). Patients with advanced cancer who had agitated delirium with a RASS of 2 or higher the past 24 hours despite being on scheduled haloperidol of 1-8 mg were included. Exclusion criteria included scheduled chlorpromazine or benzodiazepine, hepatic encephalopathy, or any contraindications to neuroleptic or benzodiazepine use. The primary outcome was RASS over the 8 hours after administration of the study medications. Secondary outcomes included neuroleptic use, delirium-related distress in nurses and caregivers (delirium experience questionnaire), symptom expression (Edmonton Symptom Assessment Scale), delirium severity (Memorial Delirium Rating Scale), need for neuroleptics, delirium recall (delirium recall questionnaire [DRQ]), adverse effects, discharge outcomes, and survival.

Clinical Practice Guidelines

Given the relative absence of high level evidence, practice guidelines based on expert input may provide some direction for clinicians. However, a majority of these guidelines were derived for the geriatric patient population [39], with only a handful focusing on the oncology and/or palliative care settings. In general, existing guidelines recommend haloperidol as the first-line option because it has few anticholinergic side effects, minimal cardiovascular adverse effects, less sedation compared to other neuroleptics and no active metabolites [40,41]. However, the dosing schedule, titrate scheme and second line agents vary widely among guidelines.

The National Comprehensive Cancer Network 2016 guideline recommends haloperidol 0.5-2 mg orally BID-TID as first line option for patients with mild or moderate delirium [42]. Alternative regimens include risperidone 0.5-1 mg PO BID, olanzapine 5-20 mg PO

daily or quetiapine fumarate 25-200 mg PO/SL BID. For patients with severe agitated delirium, the panel suggests the use of haloperidol 0.5-2 mg IV q1-4h PRN, olanzapine 2.5-7.5 mg PO/SL q2-4h PRN (maximum 30 mg/day), or chlorpromazine 25-100 mg PO/PR/IV q4h PRN. For patients who represent with refractory agitation, the addition of lorazepam 0.5-2 mg SC/IV q4h PRN was recommended.

The American College of Physicians–American Society of Internal Medicine End-of-Life Care Consensus Panel also recommended haloperidol as the first line agent for management of delirium in the palliative care setting [43]. The starting dose was 0.5-1 mg every 30 minutes orally/subcutaneously/intravenously, titrated to effect, with a maximum dose of 3 mg in 24 hours.

In a review of delirium in advanced cancer, Centeno et al. recommended haloperidol as first choice given at a dose of 2 mg PO or 1 mg SC q6h, with an additional dose every hour as needed for agitation or hallucinations. For very agitated delirium, dose increase or use of more sedating neuroleptics such as chlorpromazine or levomepromazine may be considered [3].

Summary

Much research needs to be conducted to optimize the management of delirium in the palliative cancer care setting, which is associated with significant morbidity and mortality. Although haloperidol is often recommended in clinical guidelines as a first line option, its clinical efficacy, risks, optimal dose, titration schedule need to be better defined. Other neuroleptics appear to have similar effect when compared to haloperidol, although it remains uncertain how neuroleptics compare to placebo for different patient outcomes. In patients who do not experience a response to low/moderate doses of front line neuroleptic therapy, treatment strategies may include escalating the dose of the same neuroleptic, rotation to another neuroleptic, or combination therapy with the addition of a second neuroleptic or other agent (e.g. benzodiazepine). Active studies are being conducted to examine these approaches.

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Key points

- Delirium is a common and highly distressing neuropsychiatric complication in the palliative cancer care setting.
- Management of delirium include (1) identifying and removing any reversible causes, (2) providing non-pharmacologic interventions such as environmental control and orientation aids, and (3) administering pharmacologic treatments for palliation.
- Haloperidol and other neuroleptics may be considered as first line pharmacologic options. More research is required to identify the optimal dosing schedule, risks and benefits.
- Treatment strategies for persistent agitation despite first line neuroleptic include dose escalation, neuroleptic rotation, and combination therapy.

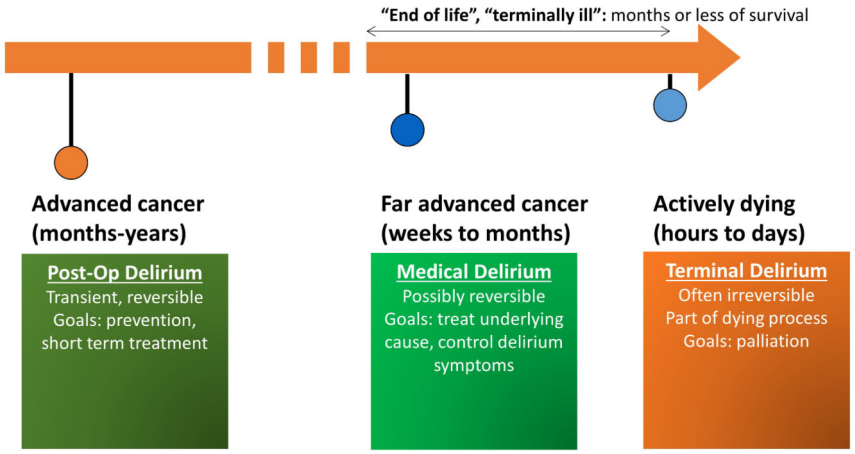

Figure 1. Prognosis-Based Decision Making

The prevalence, etiology, treatment and outcomes associated with delirium may differ substantially depending on where the patient is along the disease trajectory. For instance, patients with years of survival often have reversible types of delirium (e.g. post-operative delirium) and may be preventable, patients with months of survival may be more likely to develop delirium as a result of medical illnesses, and patients with weeks to days of survival often have terminal delirium that is not reversible.

Table 1

Randomized Controlled Trials of Pharmacologic Therapy for Delirium in Medical Settings

Authors	Setting	Sample size	Blinding	Interventions	Outcomes	Findings
Breitbart et al. 1996 [20]	Medical (HIV)	30*	Double blind	Haloperidol vs. chlorpromazine vs. lorazepam	Delirium Rating Scale Mini-Mental State Extrapyramidal Symptom Rating Scale and other side effects Karnofsky Performance status Medical Status Profile	Delirium symptoms improved similarly with haloperidol and chlorpromazine but not lorazepam.
Hu et al. 2004 [21]	Medical	175*	Open label	Haloperidol vs. olanzapine vs. no psychotropic medication	Delirium Rating Scale Clinical Global Impression Scale Treatment Emergent Symptom Scale Extrapyramidal symptom rating scale	Delirium symptoms improved similarly with olanzapine and haloperidol. Both were better than no psychotropic medication.
Han et al. 2004 [22]	Medical	28*	Double blind	Haloperidol vs. risperidone	Memorial Delirium Assessment Scale Side effects	Delirium improved significantly with both haloperidol and risperidone, with no significant between-arms differences.
Kim et al. 2010 [23]	Medical	32*	Rater blinded	Olanzapine vs. risperidone	Delirium Rating Scale Udvalg for Kliniske Undersogelser side effect rating scale	Delirium improved significantly with both olanzapine and risperidone, with no significant between-arms differences.
Tahir et al. 2010 [24]	Medical/Surgical	42†	Double blind	Quetiapine vs. placebo	Delirium Rating Scale Mini-Mental State Brief Psychiatric Rating Scale Clinical Global Improvement Abnormal Involuntary Movements Scale	Delirium improved with both quetiapine and placebo, with no significant between-arms differences in delirium scores. However, quetiapine group improved faster than placebo.
Grover et al. 2011 [25]	Medical/Surgical	74*	Rater blind	Haloperidol vs. olanzapine vs. risperidone	Delirium Rating Scale Mini-Mental State Simpson Angus Scale Abnormal Involuntary Movement Rating Scale Udvalg for Kliniske Undersogelser side effect rating scale	Delirium improved significantly with haloperidol, olanzapine and risperidone, with no significant differences among treatment arms.

*Sample size justification not reported

†Stopped prematurely and underpowered

Table 2

Theoretical Advantages and Disadvantages of Dose Escalation, Neuroleptic Rotation, and Combination Therapy

Approach	Advantages	Disadvantages
Dose escalation	Maximize dose response curve Other neuroleptics may be reserved for later if needed	Some patients may be refractory to the current neuroleptic, regardless of dose High doses of the same neuroleptic may result in more severe side effects
Neuroleptic rotation	Different spectrum of coverage Clearance of metabolites from haloperidol	Different side effect (e.g. chlorpromazine may result in over-sedation, hypotension) Neuroleptic conversion ratios have not been adequately studied
Combination therapy with haloperidol and other neuroleptics or benzodiazepines	Wider spectrum of activity Each agent can be used at lower doses and thus potentially fewer side effects	Logistics of having to administer 2 agents